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(54) Title: PROCESS FOR PREPARING LEVOBUPIVACAINE AND ANALOGUES THEREOF

(57) Abstract

A process for preparing levobupivacaine, racemic bupivacaine or another N-alkyl analogue thereof, comprises chlorinating pipecolic acid hydrochloride, amidation of the resultant pipecolyl chloride hydrochloride in solvent, without isolation, with 2,6-dimethylaniline, and alkylation of the resultant pipecolic acid 2,6-xylidide. Alternatively, the alkylation may be followed by the amidation.

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PROCESS FOR PREPARING LEVOBUPIVACAINE AND ANALOGUES THEREOF

Field of the Invention

This invention relates to a novel process for the manufacture of racemic bupivacaine or levobupivacaine, and analogues thereof, from pipecolic acid.

Background to the Invention

Bupivacaine (formula I in Scheme 1) and ropivacaine are well-known local anaesthetics. They are described in US-A-4695576, GB-A-1166802, and PCT/NO83/00029. The corresponding N-methyl and N-cyclopropyl compounds also have such activity. However, the production of such material on a large scale, from pipecolic acid, suffers from various difficulties.

Phosphorus pentachloride has been used as a chlorinating agent. On a large scale, its use is problematic, in that PCl_5 is liable to react with atmospheric moisture, and to generate waste whose separation from the acid chloride intermediate (II) is difficult. Furthermore, the phosphate waste streams which are generated are difficult to treat or otherwise discard.

The use of acetyl chloride as the process solvent for the production of the acid chloride (II) poses similar difficulties.

Whereas isolation of the intermediate acid chloride (II) as described in the art can be carried out on a laboratory scale, its isolation on the larger scale is impractical. This is due to the fact that the intermediate (II) is a very labile substance and may decompose upon exposure to atmospheric moisture.

Washing of the isolated acid chloride (II) with commercial grade acetone, as described in the art, will lead to its decomposition, as commercial acetone usually contains some water.

Reaction of the acid chloride (II) with 2,6-dimethylaniline in a mixture of acetone and N-methylpyrrolidone (NMP), as advocated in the art, leads to

the formation of pipecolic acid 2,6-xylidide (III) which is difficult to isolate from the reaction medium.

Alkylation of the intermediate (III) with 1-bromobutane and potassium carbonate in n-butanol affords comparatively poor yield of the desired bupivacaine, since the reaction proceeds very slowly and usually does not go to completion.

Summary of the Invention

The present invention describes a practical and streamlined one-pot process which is both economical and viable for scale-up. Furthermore, this invention may be used to manufacture racemic bupivacaine, levobupivacaine, or any corresponding N-alkylated material such as ropivacaine (Pr rather than Bu) in racemic or enantiomeric form.

According to this invention, pipecolic acid is initially reacted with hydrogen chloride in a suitable solvent, furnishing pipecolic acid hydrochloride salt.

This compound is not isolated from the reaction medium but is directly treated with thionyl chloride, whereupon pipecolic acid chloride hydrochloride (II) is produced. Other chlorinating agents may be used, provided that they do not contain phosphorus, e.g. oxalyl chloride.

Again, this intermediate is not isolated and is conveniently treated with (2 equivalents of) 2,6-dimethylaniline. This operation generates the HCl salt of the intermediate (III) which is later isolated, after work-up. By controlling the pH, the free base can be obtained, essentially uncontaminated with 2,6-dimethylaniline (which is released as the pH is increased).

Alkylation of the free base of intermediate (III) is carried out with an alkylating agent such as 1-bromobutane in a suitable solvent such as acetonitrile (ACN) or advantageously in dimethylformamide (DMF) in the presence of a suitable base such as potassium carbonate. The reaction proceeds rapidly, and the resulting free base of, say, bupivacaine is isolated after removal of the solvent.

The free base may then be dissolved in a suitable solvent such as isopropanol and treated with hydrogen chloride, affording the HCl salt of, say, bupivacaine which is recovered by filtration (see Scheme 1).

It appears that no significant racemisation occurs during this novel process. Therefore, for example, by using enantiomerically pure (S)-pipecolic acid in this process, levobupivacaine can be produced.

Description of the Invention

The process of the invention is carried out by the steps described above. If desired, alkylation may precede amidation. An alternative preparation of the free base (III) is described in our International Patent Application No. PCT/GB95/02385.

The following Examples illustrate the invention.

Example 1 Pipecolic acid 2,6-xylidide

Pipecolic acid (130 g) was suspended in 2 l toluene and was stirred at ambient temperature. Hydrogen chloride (40 g) was added slowly during 30 minutes.

The mixture was heated to 55°C and 1 g of DMF was added, followed by the addition of thionyl chloride (120 g) during 1.5 hours. The stirring at this temperature was continued until evolution of gases ceased.

2,6-Dimethylaniline (242 g) in toluene (250 ml) was added to the mixture at such a rate that the temperature of the mixture was maintained below 60 °C. After 2 hours, the mixture was filtered and washed with toluene (200 ml). The resulting solid was dissolved in water (2.5 l) and was treated with aqueous NaOH until its pH was raised to 4.5-5.5. The liberated 2,6-dimethylaniline was removed by extraction with toluene.

The pH of the aqueous layer was raised still further, to 11-12, whereupon pipecolic acid-2,6-xylidide (III) was liberated. This intermediate was extracted with toluene and was obtained after removal of the solvent as a crystalline solid (151 g, 65% of theory).

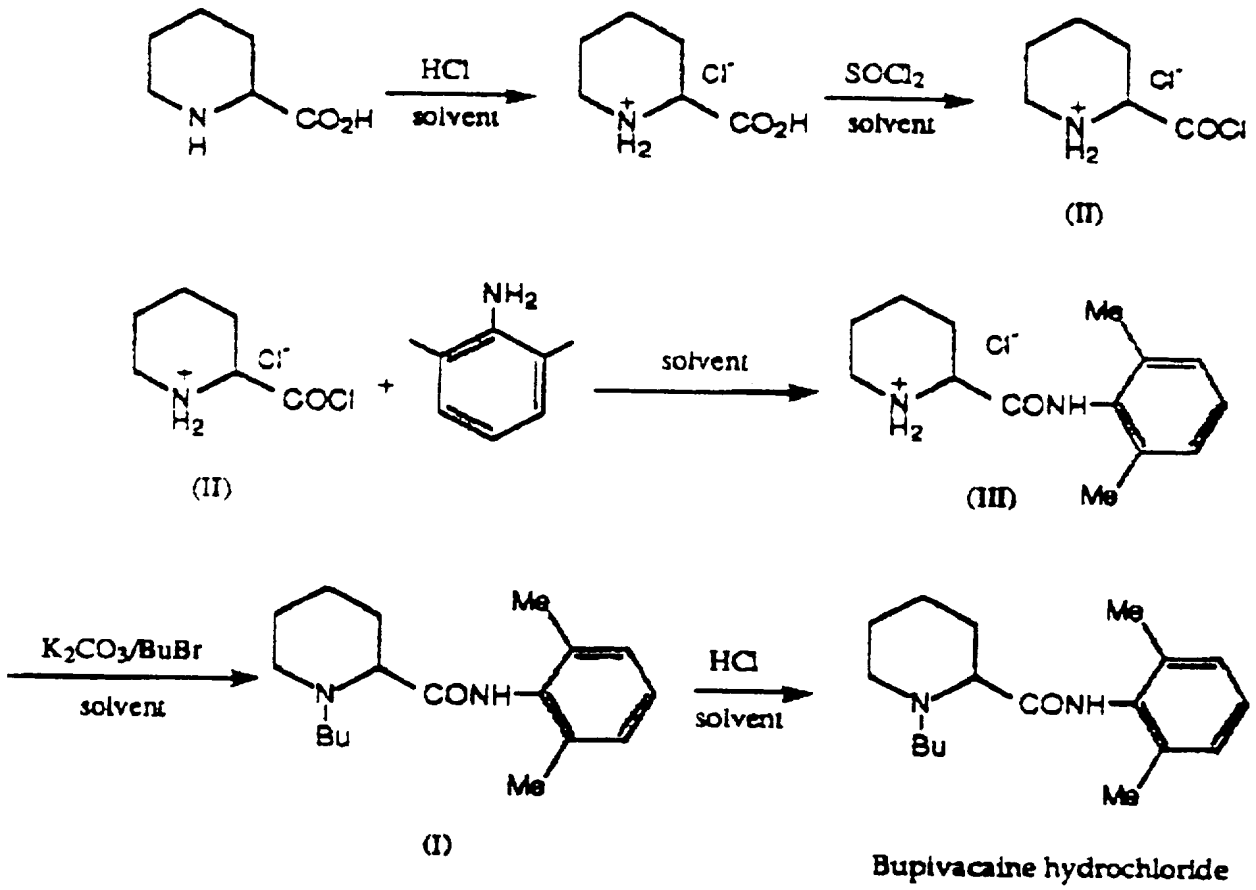
Example 2 N-n-Butylpipecolic acid 2,6-xylidide

1-Bromobutane (90 g) was added to a suspension of pipecolic acid-2,6-xylidide (140 g) and a potassium carbonate (100 g) in DMF (330 ml). The mixture was stirred and heated at 80°C for 90 minutes and then was allowed to cool to 35°C. The solids were filtered off and the DMF solution was added to cold water (1.5 l) whereupon N-n-butylpipecolic acid 2,6-xylidide precipitated as a pale cream solid (159 g, 92% theory).

Example 3 N-n-Butylpipecolic acid 2,6-xylidide HCl salt

Hydrogen chloride (25 g) was introduced slowly into a stirred solution of N-n-butylpipecolic acid 2,6-xylidide (145 g) in isopropanol (250 ml) at ambient temperature. The resulting white product was filtered off, washed with isopropanol and dried under vacuum to constant weight (161 g, 99% theory).

In order to prepare levobupivacaine, by the process of the present invention, a first route involves preparing and then resolving racemic bupivacaine. A racemisation process is described in International Patent Application No. PCT/GB95/02247. A second route involves starting from the appropriate pipecolate enantiomer.



Scheme 1: A Novel Method for the Manufacture of Bupivacaine

CLAIMS

1. A process for preparing bupivacaine or another N-alkyl analogue thereof, which comprises the following steps:

reaction of pipecolic acid hydrochloride with a P-free chlorinating agent in a solvent;

either amidation of the resultant pipecolyl chloride hydrochloride in solvent, without isolation, with 2,6-dimethylaniline, and alkylation of the resultant pipecolic acid 2,6-xylidide; or the alkylation followed by the amidation;

if desired, conversion of the resultant bupivacaine or analogue, as the free base, to a salt thereof; and

isolating the product from the reaction mixture.

2. A process according to claim 1, wherein the solvent for said chloride hydrochloride is an inert solvent having a boiling point that enables the removal of excess chlorinating agent optionally together with HCl, by distillation.

3. A process according to claim 2, wherein said inert solvent is a hydrocarbon, halogenated hydrocarbon or ether, more specifically toluene, methyl tert-butyl ether, tetrahydrofuran, DMF or acetonitrile.

4. A process according to any preceding claim, wherein the solvent for the alkylation solvates K_2CO_3 and is water-miscible.

5. A process according to claim 4, wherein said water-miscible solvent is DMF.

6. A process according to any preceding claim, whereby (S)-pipecolic acid is converted to levobupivacaine.

7. A process according to any of claims 1 to 5, wherein the product is racemic bupivacaine.

8. A process according to any of claims 1 to 5, wherein the product is 1-propyl-N-(2,6-dimethylphenyl)-2-piperidine-carboxamide, in racemic or optically-enriched form.

9. A process according to any preceding claim, wherein the amidation precedes the alkylation.

10. A process according to any preceding claim, wherein the chlorinating agent is $SOCl_2$.

11. A process according to any preceding claim, wherein, following amidation, the product is separated from 2,6-dimethylaniline by raising the pH.

INTERNATIONAL SEARCH REPORT

Interna ... Application No
PCT/GB 95/02514

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07D211/60

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO,A,85 00599 (APOTHEKERNES LAB. FOR SPECIALPRAEPARATER) 14 February 1985 cited in the application see the whole document ---	1-11
A	US,A,4 695 576 (ASTRA) 22 September 1987 cited in the application see example 2 ---	1-11
A	J. MED. CHEM., vol. 34, no. 1, 1991 pages 397-403, V. VECCHIETTI ET. AL. '(2S)-1-(Arylacetyl)-2-(aminomethyl)piperidine Derivatives: Novel, Highly Selective k Opioid Analgesics' scheme 1 see page 398 ---	1-11

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

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Date of the actual completion of the international search	Date of mailing of the international search report
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Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+ 31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+ 31-70) 340-3016	Henry, J

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(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	S.S. PIZEY 'Synthetic Reagents, Vol I, Chapter 4' , JOHN WILEY AND SONS INC. , NEW YORK, LONDON, SYDNEY, TORONTO see page 333 - page 336	1-11

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Interm al Application No
PCT/GB 95/02514

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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		AU-B- 1779683	04-03-85
		EP-A,B 0151110	14-08-85
		JP-T- 60502054	28-11-85
US-A-4695576	22-09-87	NONE	